Guidelines and recommendations for assessment of somatosensory function in oro-facial pain conditions - a taskforce report

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Abstract: Summary The goals of an international taskforce on somatosensory testing established by the Special Interest Group of Oro-facial Pain (SIG-OFP) under the International Association for the Study of Pain (IASP) were to (i) review the literature concerning assessment of somatosensory function in the oro-facial region in terms of techniques and test performance, (ii) provide guidelines for comprehensive and screening examination procedures, and (iii) give recommendations for future development of somatosensory testing specifically in the oro-facial region. Numerous qualitative and quantitative psychophysical techniques have been proposed and used in the description of oro-facial somatosensory function. The selection of technique includes time considerations because the most reliable and accurate methods require multiple repetitions of stimuli. Multiple-stimulus modalities (mechanical, thermal, electrical, chemical) have been applied to study oro-facial somatosensory function. A battery of different test stimuli is needed to obtain comprehensive information about the functional integrity of the various types of afferent nerve fibres. Based on the available literature, the German Neuropathic Pain Network test battery appears suitable for the study of somatosensory function within the oro-facial area as it is based on a wide variety of both qualitative and quantitative assessments of all cutaneous somatosensory modalities. Furthermore, these protocols have been thoroughly described and tested on multiple sites including the facial skin and intra-oral mucosa. Standardisation of both comprehensive and screening examination techniques is likely to improve the diagnostic accuracy and facilitate the understanding of neural mechanisms and somatosensory changes in different oro-facial pain conditions and may help to guide management.

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Guidelines and recommendations for assessment of somatosensory function in orofacial pain conditions – a taskforce report

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Abstract

The goals of an international taskforce on somatosensory testing established by the Special Interest Group of Orofacial Pain (SIG-OFP) under the International Association for the Study of Pain (IASP) were to 1) review the literature concerning assessment of somatosensory function in the orofacial region in terms of techniques and test performance, 2) provide guidelines for comprehensive and screening examination procedures, and 3) give recommendations for future development of somatosensory testing specifically in the orofacial region. Numerous qualitative and quantitative psychophysical techniques have been proposed and used in the description of orofacial somatosensory function. The selection of technique includes time considerations because the most reliable and accurate methods require multiple repetitions of stimuli. Multiple stimulus modalities have been applied to study orofacial somatosensory function (mechanical, thermal, electrical, chemical). A battery of different test stimuli is needed to obtain comprehensive information about the functional integrity of the various types of afferent nerve fibers. Based on the available literature, the German Neuropathic Pain Network test battery appears suitable for the study of somatosensory function within the orofacial area as it is based on a wide variety of both qualitative and quantitative assessments of all cutaneous somatosensory modalities. Furthermore, these protocols have been thoroughly described and tested on multiple sites including the facial skin and intraoral mucosa. Standardization of both comprehensive and screening examination techniques is likely to improve the diagnostic accuracy and facilitate the understanding of neural mechanisms and somatosensory changes in different orofacial pain conditions and may help to guide management.

Introduction

Assessment of somatosensory function is believed to provide important information on the mechanisms underlying various pain conditions (1,2). For example, after injury to the somatosensory system, pain may be evoked by innocuous stimuli, such as brushing the skin (dynamic mechanical allodynia), or there can be increased pain to stimuli that normally cause pain (hyperalgesia), such as pinprick. In addition to these painful, positive signs (gain in function), injury to somatosensory pathways may also produce negative signs (loss of function) such as hypoesthesia or anesthesia (2), although the negative signs may be difficult to detect in routine clinical examination (3,4). Recently, a grading system of certainty for neuropathic pain has been proposed (Table 1). Examination of somatosensory function within the distribution of pain plays a pivotal role in the certainty of the diagnosis (2,5). Quantitative sensory testing (QST) can be used along with bedside testing to document the somatosensory profile (5). Since somatosensory abnormalities have often been reported in non-neuropathic pain conditions as well, QST alone cannot be considered sufficient to differentiate between specific pain conditions (5). However, QST is helpful to quantify the effects of treatments on for example allodynia and hyperalgesia (5).

One of the challenges of somatosensory testing is to use adequately standardized stimuli that selectively activate different classes of the nerve fiber populations (i.e., A-beta, A-delta and C-fibers) (1). Thus, a comprehensive profiling of somatosensory dysfunction will require multiple stimulus modalities. A second challenge of valid somatosensory testing pertains to the reliability of obtained information, because there is variation related to stimulus application, to the method by which the testing is done, and to the subjects´ ability to report their sensations consistently. Recently the German Research Network on Neuropathic Pain (DFNS) published a series of papers which described and tested a comprehensive assessment protocol for different body regions including the face (cheek) (6-9). Many of the techniques used to study somatosensory function on

other parts of the body can also be adapted to the orofacial region, but the physical dimension, the small size of trigeminal distributions, and the specific topography of the oral cavity and the facial region impose constraints in the study of trigeminal somatosensory function.

The Special Interest Group of Orofacial Pain (SIG-OFP) under the International Association for the Study of Pain (IASP) has initiated an international taskforce on somatosensory testing specifically related to the orofacial region. The aims were first, to review the literature concerning assessment of somatosensory function in the orofacial region in terms of techniques and test performance (e.g. duration, reproducibility), and second to provide guidelines for both screening and comprehensive examination procedures. The final aim was to give recommendations for future development of somatosensory testing in the orofacial region.

Literature search

The literature was searched with the use of PubMed and the following MeSH terms: quantitative somatosensory testing or neurosensory testing or somatosensory function and – orofacial or – trigeminal or – craniofacial - or facial. In addition, papers identified by international experts and members of the SIG-OFP were included. The intention was, however, not to perform a systematic review according to QUADAS criteria (10) because diagnostic accuracy of orofacial pain conditions is the topic of a separate SIG-OFP taskforce.

Draft versions of the guidelines and recommendations for orofacial somatosensory testing were reviewed by members of the Neuropathic Pain SIG (Rolf-Detlef Treede, Doreen Pfau, and Ralf Baron) and revised before submission.

Review of psychophysical principles

In order to investigate somatosensory function quantitatively in humans, two basic prerequisites are needed. First, a stimulus that can be controlled and characterized in terms of specific somatosensory modality, stimulus location and size (spatial characteristics), stimulus duration and frequency (temporal characteristics) and stimulus magnitude (physical intensity). Second, a quantitative measure of the stimulus-evoked response must be obtained, and this can either be a subjective verbal or non-verbal report (psychophysical response), a neurophysiological signal (e.g. compound sensory nerve action potentials, reflex responses, somatosensory evoked potentials) or a relevant physiological response (e.g. change in blood flow, skin temperature, heart rate). In this review we will only focus on psychophysical techniques and the reader is referred to other recent reviews of relevant neurophysiological and other physiological techniques (e.g. 11-15). It is also beyond the scope of this publication to review the use of psychophysical principles in the study of endogenous pain modulatory systems by simultaneous application of conditioning and test stimuli of different modalities (16).

Psychophysics has, for more than a century, been a powerful tool in neuroscience to investigate human sensory systems including those associated with vision, hearing, olfaction, taste, equilibrium and somatosensation (17-22). The general concepts and assumptions in threshold estimation and psychophysical scaling also apply to the study of somatosensory function in the orofacial region. For an exhaustive review of psychophysics the reader is referred to Gescheider 1997 (23). In the following paragraphs, a brief review of the most applicable techniques used in the quantitative assessment of sensory function (quantitative sensory testing, QST) in the orofacial region is provided.

Threshold determination

A fundamental concept in psychophysics is that of threshold. Simply stated, threshold is the minimal level of energy needed to evoke a subjective sensation, i.e. to be detected. Accordingly, thresholds are reported in terms of stimulus values, such as temperature levels (in °C) or mechanical forces (kg equivalent weight, or Newtons) (24). A thermal threshold, for example, is typically defined as an absolute warm detection threshold or cool detection threshold (^{o}C), i.e., the temperature most similar to the resting skin temperature at which the targeted sensation is detected by the subject. Instead of absolute thresholds, a rougher estimate of temperature sensitivity can also be measured as a warm-cold difference limen (i.e., the range of temperature between warm and cool detection thresholds; also called the Marstock method). Sensory detection thresholds such as these, pain detection thresholds, pain tolerance thresholds, and pain summation thresholds have all been used extensively to characterize the altered thermal sensibility in patients with pain (Table 2). In principle, determination of psychophysical thresholds requires that the test subject, with the highest possible degree of certainty, and not simply by guessing, detects the stimulus and makes a conscious decision as to whether the stimulus fulfilled the criteria for the response option(s). Stimuli of different intensities are applied in a manner dictated by the psychophysical paradigm. Several stimulus presentation paradigms (also called testing algorithms) may be used in QST (e.g., 25-29).

The *method of constant stimuli* is the classical psychophysical paradigm to determine an absolute threshold, e.g., the detection threshold for thermal or tactile sensations. The procedure repeatedly uses the same set of stimuli; for example, between five and nine different levels of a stimulus (e.g. temperature or force) throughout the experiment. The test subject responds to each of the thermal or mechanical stimuli by "yes" (detection) or "no" (no sensation) and a psychometric

function is constructed by plotting the proportion of "yes" responses versus the stimulus intensity, which creates a stimulus-response curve (Fig. 1). The detection or sensory threshold is defined typically as the stimulus intensity detected in 50% of the trials, although other definitions have also been used. The psychometric curves are usually S-shaped or ogive and can be subject to mathematical analysis for estimation of the threshold and its confidence interval (23). The method of constant stimuli is considered to be a very exact method but requires numerous replications of each stimulus level, is therefore time-consuming, and is often not feasible for routine analysis of somatosensory function. In addition, the accuracy of detection threshold determination with this technique depends on the overall range of and the difference between the stimulus levels chosen for the paradigm.

The *method of limits* requires much less time than the method of constant stimuli or method of levels, and embraces a number of psychophysical techniques such as the ascending-descending method, the staircase method, and other sequential threshold-tracking methods (30). Variations of the techniques are dictated by the characteristics of the stimulus. For example in these techniques, as well as the estimated threshold, one major distinction is whether discrete stimuli (e.g. a 5-s pulse of a fixed intensity) are applied or if gradually, linearly increasing (or decreasing for cold) intensity levels are applied. Method of limits with linear change in stimulus intensity is at present available in most commercial devices for the estimation of thermal and vibratory detection thresholds. In this approach, the stimulus intensity begins to increase from a thermoneutral baseline (thermal) or zero (vibration) and the subject indicates the detection by pushing a button or by a verbal report after which the stimulator returns back to baseline, and the next stimulus begins after a random interval. Mean or median of the stimuli at which the response occurred is calculated as the detection threshold. The method of limits with discrete, stepwise stimuli is mainly used for tactile detection threshold tracking with calibrated monofilaments where alternate ascending and descending series

of discrete stimuli can be used, after each of which the subject responds "yes" or "no" as to detecting the sensation of interest (warm, cool, touch, or pain). The transition point is taken midway between the last "yes" response and the first "no" response (Fig. 2A). The threshold is then calculated as the average of the transition points. Depending on the up-and-down transform rules used, this stimulation paradigm may require fewer stimuli than the method of constant stimuli but is more sensitive to habituation and expectations. A variation of methods with discrete, constant level thermal or mechanical stimuli is the method of levels or *sequential testing* adopting different kinds of up-and-down transform rules (UDTR) to change the intensity of consecutive stimuli in a series e.g. *staircase* method. With these methods, a sequence of constant level stimuli is presented with predetermined rules to progressively increase or decrease the intensity level until the response of the test subject is changed, after which the stimulus intensity is reversed. The threshold is described as the arithmetic or geometric mean of several transition points (Fig. 2B). Attempts have been made to construct a multiple random staircase paradigm in order to reduce subject habituation and expectation effects (31).

The alternative approach to the method of limits involves applying a gradually increasing stimulus, while the subject is instructed to push a button to signal his or her perception of the sensation of interest (Fig. 3) and is thus a *reaction time inclusive method*. The advantage of this method of limits testing is a very fast and simple paradigm but the threshold can be overestimated due to the reaction time delay, during which the temperature or mechanical force continues to change. The magnitude of the error will be affected by the conduction velocity of the class of thermoreceptors or nociceptors tested and the rate of stimulus change; however, with slower rates of changes (e.g. 0.5-1 ℃/s for temperature) the effect of reaction time error can be reduced. Yarnitsky and Sprecher 1994 (32) compared the method of limits, classical method of levels and its staircase variation for determination of warm and cool detection thresholds and found significantly less

between-session variability and better repeatability for the latter two techniques that adopt constant level stimuli and represent the *reaction time exclusive QST methods* that, however, require longer testing times than the reaction time inclusive method of limits (29).

Finally, but less frequently, the *method of adjustment* has been used to characterize thermal sensitivity. In this method the subjects themselves adjust the intensity of the stimulus to the threshold level. The method has the advantage to reduce boredom and to engage the subject more actively in the threshold determination.

Most psychophysical techniques are sensitive to parameters such as the interstimulus interval, step size (i.e, differences in the stimulus intensity levels), stimulus duration, stimulation frequency and number of trials. The total duration of testing session is also an important factor, as vigilance and attention play a major role in getting reliable psychophysical test results (33, 34). In assessment of thermal sensitivity, parameters such as baseline skin (and oral) temperature, ambient room temperature, and rate of temperature change also will affect the results (24, 35). These parameters therefore need to be described and standardized. The main advantage with the stimulus-dependent techniques is that the threshold is expressed in physical units of the stimulus or duration of application (seconds, ^{o}C, watts, joules, N, gram etc) and that they often require fewer stimuli than the other main group of psychophysical approaches: suprathreshold scaling (see below). Thus, they are generally faster (2–3 min for a single threshold determination), can be used to monitor somatosensory function over time, and are considered suitable for routine neurological screening. Subject bias is, however, always a concern in psychophysical assessment of thresholds, although it is less prominent for non-painful sensory thresholds than for pain thresholds (24). This is readily observed in thermal thresholds: the detection thresholds of warm and cool are less variable between subjects than those for the heat and cold pain, cold pain thresholds being particularly variable among subjects (36).

Response bias is one contributor to this larger variation in pain thresholds, as demonstrated by Yarnitsky and colleagues in 1994 (37). Healthy volunteers were instructed to pretend a somatosensory disturbance and found that these "feigning" subjects had larger variance of the warmth detection threshold than "trustworthy" subjects and neuropathic pain patients. As another example, individuals with autism have been found to exhibit lower heat pain thresholds than control subjects; however, the difference is less when measured on a second day (38). These examples illustrate the importance of a thoughtful assessment as to whether changes in estimates of the threshold are best attributed to changes in sensory discrimination versus changes in response bias. In some instances, blank stimuli or "sham" stimuli can be inserted into the series of stimulus presentation as a check of subject bias and performance (28). Alternatively, the threshold can be estimated using a forced choice method.

The *forced choice method* represents a modification of a psychophysical technique and provides a measure of stimulus detection or discrimination that is not influenced by the subject's response criterion (23, 25). In this method, during each trial two or more stimuli or intervals during which stimuli might be delivered are provided from which the subject can choose. The forced choice method is used in concert with the methods of constant stimuli and levels, and of sensory detection. The major limitation of this method is the very long time it takes to determine a single threshold (27). In addition, it has been considered psychologically stressful due to its sustained task demand, and not suitable for clinical patient diagnostics (29).

Finally, it has been argued that the powerful analysis method of *sensory decision theory* (38, 39), based on a more general signal detection theory (SDT) introduced in the late 1940's (e.g. 40), could be used in QST studies. According to the SDT, sensory discriminative capacity and subjective response criterion (i.e., response bias) are calculated separately, which enables detailed assessment of both factors independently, and analysis of their respective roles in, for instance, treatment

effects on sensory thresholds. SDT thus yields two measures that determine perceptual performance. The discriminability measure reflects the accuracy with which the test subject judges whether the event "A" or event "B" has occurred. The report criterion measure quantifies the subject's response bias, which is the general tendency to report one of the events as occurring more frequently than the other. Event "A" could be a high-intensity thermal stimulus (hot) and event "B" a low-intensity thermal stimulus (warm). After each stimulus presentation the subject decides whether "A" or "B" has occurred and the four decision options can be arranged in a 2 x 2 matrix (Fig. 4). In the study of pain thresholds with SDT, several levels of stimulus intensities can be adopted and similarly mathematically treated to extract the relative contributions of sensory discriminative capacity and subjective response criterion to the measured pain thresholds (34). Clark (38) has argued strongly for the use of SDT and made several important points to its applicability in QST. However, a large amount of data must be collected in order to determine the distributions and even though detectability and discriminability are important features of somatosensory function, other assets like the character or quality or subjective intensity are not assessed (28). Therefore, and also given the time required for the SDT method, it is not likely to be the first method of choice when somatosensory function of orofacial region is assessed in clinical settings. However, in research settings, it offers an interesting tool for in-depth-analysis of the factors contributing to clinical pain conditions and treatment effects on e.g. pain thresholds (23, 38). SDT has also been applied to the study of modulation of facial thermal pain sensitivity with repetitive transcranial magnetic stimulation (rTMS), which showed that rTMS given to different cortical target sites had discrete effects on sensory discriminative capacity or subjective criterion, depending on the site of stimulation (34).

Suprathreshold intensity ratings

The essential feature of this type of psychophysical technique is that a fixed stimulus is applied and the test subject judges the perceived intensity (or affective quality) of the stimulus using a rating scale. Thus, the subjective magnitude estimation is considered the dependent variable (24). Usually, several different stimulus intensities are used and applied several times in randomized order, which avoids confounds associated with time or order. In this way, it is possible to construct psychophysical stimulus-response (S-R) curves which then are available for mathematical modeling and analysis. Measurement scales can either be nominal (for identification and classification), ordinal (for rank order), interval (for distances or differences) or ratio (for ratios and fractions).

Visual analogue scales have been shown to possess ratio-scale properties (41) and are widely used in pain psychophysics (24), and can also be used to rate non-painful thermal or mechanical sensations (Fig. 5) (42-44). In the simplest form a 100-mm visual analogue scale with endpoints like “no pain” to “worst pain imaginable” or “not warm at all” and “extremely warm” can be used (45). Alternatively, ordinal numerical rating scales (NRS) can also be used for stimulus magnitude estimation (eleven points from 0 to 10). The NRS necessarily provides for a measure with less resolution than a VAS, but not necessarily less accurate (46). Various forms of verbally labeled category scales have also been developed to assist the test subjects in the scaling procedure (47-49). These scales look similar to visual analogue scales, but have word descriptors (e.g., “moderately painful”) at positions along the numerical scale that have been determined experimentally. Despite what may seem to be cosmetic differences among these different scales, there are conceptual and functional differences that one must consider when employing or interpreting results using these scales (46, 50). Another approach to measuring suprathreshold perceptions is the use of magnitude estimation scales where “free numbers” are allowed (21, 51). This avoids the problem of bounded scales where subjects may tend to spread their ratings

throughout the scale and as a consequence scaling is sensitive to stimulus range and spacing (24). For magnitude estimation, a standard stimulus may be presented and the test subject told to assign a certain number to this stimulus, e.g., 20 which then is termed the modulus (44, 52). The following stimuli are rated relative to the modulus, thus if the next thermal stimulus was perceived as twice as intense as the first, the test subject should assign the number 40. Usually, the median or geometric mean is calculated since the average can be influenced by a few unrepresentative high judgments. Magnitude estimation has been used in some studies on somatosensory function in the orofacial region (e.g. 53-56).

The main advantage of the magnitude estimation techniques is a more composite measure of somatosensory function than a single sensory detection or pain threshold would provide (slope of the S-R curve including estimates of absolute thresholds) (23). However, many more stimuli (4–5 repetition per intensity level) are normally needed in order to construct the S-R curves and it may be more time-consuming and may not allow for tracking of fast changes in somatosensory function during experimental manipulations. Moreover, the slopes of the S-R curves are subject to individual differences among subjects as well as modes of stimulation (44). For example, the S-R curves for thermal stimuli ranging from the non-painful to the painful range applied to the skin above the masseter muscle can be fitted by power functions in accordance with the power law (21, 57). This is in agreement with several other observations on thermal sensations in the orofacial region (53, 54, 58). However, radiant and contact heat stimulation yields power exponents (slope of curve in a log-log plot) close to 1 and 2, respectively suggesting that the conduction of heat and activation of thermoreceptors differ with the two types of heat stimulation (58, 59). Interestingly, S-R curves may also be influenced by the curve-fitting procedures. For example, classical psychophysics predict a power function for thermal stimuli ranging from warm to heat pain and the power exponent is in the range of 2.1 (57). However, a careful evaluation of the transition zone from heat

to heat pain revealed that two linear regression lines could equally well be fitted, with slopes significantly lower in the non-pain range compared to the painful range (60). Similar observations have been made on the lip and tongue (53). Great care should therefore be taken to check the actual best fit of S-R curves when somatosensory function in the orofacial region is analyzed.

Mapping

Mapping procedures attempt to outline the extent of an area with somatosensory alterations. Usually, a qualitative, clinical approach with a fixed stimulus intensity (e.g., a cotton swab or a von Frey filament) is used and the subject asked to respond in a dichotomous way to the question of "altered sensation". The area can then be outlined by marking the borders between "normal" sensation and "changed sensation" (Fig. 6). A cold or warm "thermoroller" (Fig. 7) can be used in addition to mechanical stimuli (1). Such techniques have been used to outline primary and secondary hyperalgesic areas or hyposensitive areas in experimental and clinical conditions (44, 61-63). Mapping is considered a pivotal approach in the survey of the somatosensory system pathology (1) and it is an advantage that the area can be quantified and followed over time (61, 64). Mapping procedures are obviously more challenging to perform intraorally but can be attempted. So far no data are available on the reliability of intraoral mapping techniques.

A variation of this method is to stimulate at fixed sites in a grid, e.g., every 1 cm, and to have the subjects to rate the intensity of the stimulus. This will allow center-of-gravities (COG) to be determined as a measure of both the extent and intensity of sensory function (65, 66). This technique can be used to provide a comprehensive description of the spatial and intensity dimensions of sensory function in a neuroanatomically defined area, e.g., the infraorbital region.

In summary, several stimulus- and response-dependent techniques are available for the psychophysical assessment of somatosensory function in the orofacial region (14, 67-73). The more robust techniques are usually more time-consuming, making the choice of technique dependent on the specific purpose and time and equipment available for the study. However, any psychophysical measure will inherently be susceptible to subject bias and the test paradigm should therefore try to minimize this component. A number of other parameters like gender of the investigator, instruction provided to the test subject, attention, distraction, habituation as well as vigilance, cognitive capacity and motor performance of the test subject or patient must all be considered since they are potential confounds of the outcome (24). In addition, environmental conditions like room temperature, illumination, and noise level should be kept as constant and comfortable as possible to reduce distractive elements disturbing the test process. Nevertheless, valuable insight into the characteristics of somatosensory function in the orofacial region can be obtained, provided that a sound and validated psychophysical technique is used and reliable reference values (normal values) for the QST procedure have been obtained.

Stimulus modalities

This section will begin with a brief review of the many and often ingenious stimulators developed and used in the orofacial region. The stimulators are categorized according to the stimulus and somatosensory modality (Table 3).

Mechanical stimulation

There is consensus that different types of mechanical hyperalgesia can be distinguished in neuropathic pain conditions and that these can be assessed qualitatively or semi-quantitatively by different types of mechanical stimulation applying magnitude estimation techniques (74-76). Static

allodynia may be evoked by gentle pressure to skin; punctate hyperalgesia, by punctate stimuli such as pin-prick or nylon filaments; and dynamic allodynia, by light brush strokes. Finally, there may be hyperalgesia to impact stimuli (shooting small bullets against the skin at predetermined velocities) (75). Different neural mechanisms have been shown to underlie these different types of mechanical hyperalgesia. Therefore there is a need to apply different types of mechanical stimuli in a comprehensive analysis of somatosensory function (Table 3).

Tactile stimulation

Calibrated von Frey nylon monofilaments (Semmes Weinstein aesthesiometers) with forces ranging from 4mg to 300g weight have frequently been used for quantitative assessment of tactile sensitivity within the orofacial region (3, 4, 68-70, 73, 77, 78). The filament is applied vertically to the test site, and pressure is slowly increased until a single bend in the filament is observed, signifying delivery of the calibrated force (79). The time needed to bend the filament can be standardized to about 1–2 s and stimulus maintained for 1–2 s and then removed (80, 81). An issue with nylon filaments is that they are sensitive to humidity due to the porosity of the nylon; as a result, more accurate estimates of the threshold are obtained if nylon filaments are calibrated on an electronic balance pan (79). Continuous humidity control and regular calibrations of the monofilaments (e.g. at 6 months intervals) are necessary to detect significant changes in the bending forces in time and to ensure reliable test results. In intraoral testing with nylon monofilaments, humidity may significantly influence the test results and it has been suggested that optical glass fiber filaments are better (82). Another issue is that the instruments that are commercially available were not designed for use on the orofacial region and only a few filaments are useful on the more sensitive sites. E.g., the force delivered by the finest filament (approximately 5 mg weight; filament marked ‘1.65’) is often detected, whereas the force of the second finest filament (approximately 23

mg weight; filament marked '2.36') is detected at many orofacial sites in the absence of somatosensory dysfunction (83, 84). Electronic tactile stimulators based on strain gauge principles are also available now, but have so far mainly been used in animal experiments (e.g. 85, 86).

A range of other types of tactile stimuli has been proposed and used for assessment of dynamic mechanical sensitivity, for example, brushing the skin with feathers, cotton swabs, or commercially available brushes with standardized bending forces, and vibrating the skin with the bristles of an electrical toothbrush. Stroke-brush direction or directional sensitivity can provide information on complex spatiotemporal patterns of mechanoreceptor activation for example during speech. It can be assessed as a percentage of correct answers about a brush being moved in a medial to lateral or lateral to medial direction (3, 4, 68, 87). The same innocuous stimuli can be used to assess the presence of abnormally evoked pain. For example, a cotton swab (diameter 10 mm) can repeatedly be brushed over a painful facial or intraoral region and the contralateral side for 10 s at about 2 Hz, and the increase in pain, if any, be assessed on a 0–10 VAS (78). A computer controlled automated air jet stimulator with a flow range from 2 to 20 L/min has recently been developed primarily for QST of intraoral mucosal wounds, as stimulation is possible without tissue contact (88). A modified portable version has recently been tested for assessment of oral wound sensitivity (89). Further studies are needed to clarify which sensory neurons are being stimulated with this new modality.

Vibration

Vibratory stimulation is also part of a routine neurological examination of somatosensory function (90) and can be achieved either with tuning forks or more precisely and quantitatively with electronic vibrameters where frequency and amplitude, and in some devices also pressure, can be

controlled and the vibratory detection thresholds measured (1, 91). Vibrotactile function has also been described in the face (92-95) and shown to be altered in TMD conditions (96, 97). The facial area does not, however, offer many optimal sites for quantitative analysis of vibratory detection thresholds, as the vibrating probe should preferentially be located on a surface with tight skin-bone contact without too much subcutaneous tissue. Different populations of mechanoreceptors can be selectively activated by using specific values of frequency and amplitude. Vibrotactile sensitivity can also be assessed intraorally (98-101). Vibrating bristles (electrical toothbrush) can be used to assess the temporal summation of pain. The bristles are applied over a painful facial or intraoral region and the contralateral side for 10 s, and the increase in pain be assessed on a 0–10 VAS (78). In addition, with electronic vibrameters, allodynia to vibration may be quantitatively measured, which allows accurate evaluation of e.g. treatment effects.

Two-point discrimination

This classical test consists of devices with two blunt needles separated by fixed distances ranging from 2–30 mm (102-104). Two variants of the technique have been described. The first is *two-point discrimination* which is the minimum separation between two points for which a subject discriminates two from one point of contact, whereas the second is the *two-point perception threshold* defined as the minimum separation between two points of contact for which a subject perceives two rather than one point of contact. Both thresholds are used as measures of the patient's spatial processing capacity and are related to the peripheral innervation density of the test site. However, both are less than ideal for this purpose because they are affected by the subject's use of non-spatial information and response biases (68, 105). Improved methods of assessing spatial acuity based on grating orientation (a psychophysical tracking procedure used to estimate the threshold groove width for discriminating orientation (horizontal or vertical) of square-wave gratings pressed

into the skin) and letter recognition (a simple up-down tracking procedure to assess spatial acuity on for example the tongue tip) mitigate these limitations; however, subjects are only able to perceive the stimuli on the most sensitive orofacial sites, the tongue tip and the vermilion (105, 106). Thus, the usefulness of these methods for assessing spatial acuity is limited. For the two-point thresholds, different tracking tasks and psychophysical procedures can be used and more sophisticated pressure-controlled two-point discriminators have been developed for application in the orofacial region (103, 104, 107-109). Two-point discrimination probes with constant forces can also be applied intraorally (69, 70).

Pin-prick

The simplest way to qualitatively assess pin-prick sensitivity is to use a pin (1). However, in a similar way as described above for tactile stimulation, thicker von Frey filaments or force calibrated pins can be used to quantitatively determine a pain detection threshold, that is, the least force for which the subjects will report a painful sensation in, for example, 50% or75% of the applications (78). Modified dental explorers can be used for assessment of pin-prick sensitivity intraorally (52, 110, 111). More elaborate constant force stimulators (weighted needles) have also been developed mainly for application of punctate stimuli (6, 7, 112-114). Importantly, in addition to the force applied, shape, size, and angulation of the probe will influence the assessment of mechanical pain detection thresholds (112) and should be standardized and controlled (orthogonally to the test area). Electronic von Frey stimulators may also be possible to use to determine pin-prick sensitivity.

Pinch

Pinch-stimuli can be applied using constant-force forceps (115, 116) as well as more simple commercially-available clips (117). In these cases, the dependent variable is a pain rating on a VAS or NRS. Also the use of certain types of pressure algometers can be used to pinch orofacial tissues and to determine a pinch-evoked pain threshold (118-120).

Deep pressure

Pressure algometry is a commonly used QST technique and has been used extensively in clinical and experimental pain studies (121-128). Multiple types of pressure algometers have been developed (124). The most simple allow assessment of pressure using pressure-sensitive devices fitted to the finger (i.e. palpometers) (127, 129). Hand-held devices based on spring coil systems are also frequently used (124, 130). The more sophisticated pressure algometers provide visual feedback on the pressure application rate which has been shown to influence the pain threshold (131). Servo-controlled pressure devices with constant application rates have also been developed but have not yet been tested clinically (132, 133). The pressure (i.e. force per area often expressed in kPa) that the participants first perceive to be painful is defined as the pain threshold and the maximum pressure endured by the participants is defined as the tolerance threshold. Different pressure algometers have also been applied to intraoral tissues (134-136). Within the orofacial area, a pressure increasing at a rate of 50 kPa/s with a 4.8-mm diameter probe intraorally or 1.1 cm diameter probe extraorally can be applied, and the average value of three measurements calculated (101). The procedure is normally repeated three times with about 1 min between consecutive stimuli.

Other variations of mechanical stimulation

Oral stereognosis is a technique where subjects without the aid of vision attempt to identify the form of a test object applied intraorally (69, 70, 137-140). Thus, it is a composite measure of inputs from multiple mechanoreceptors in the periodontal ligament and oral mucosa in addition to mechanoreceptive inputs from jaw muscles and the TMJ (69).

The capacity for more complex spatial tactile discrimination has also been assessed within the orofacial region with the so called grating orientation test (see description above) (3, 68, 105).

Occlusal sensitivity or tactile sensibility in human teeth has traditionally been determined as the thinnest foil inserted between pairs of teeth which the subject can perceive (141, 142). It may be a measure of periodontal ligament afferent sensitivity. Also in conditions with periapical pathology, a variation with a bite-force transducer can be used as a measure of allodynia or hyperalgesia in the periodontal ligament (143).

Thermal stimulation

Some of the oldest reports on thermal sensations in the orofacial region originated from Germany more than 100 years ago (17). In these qualitative or semi-quantitative methods, copper and aluminum rods heated or cooled to various temperatures were used for a meticulous description of temperature sensitive spots (144-146). The diameter of the metallic rods ranged between 4–9 mm. This simple but straightforward stimulation technique was inevitably associated with a mechanical bias because of the concurrent activation of mechanosensitive afferent fibers in addition to the thermosensitive fibers. Furthermore, the amount of pressure and temperature change during tissue contact was not easily controlled. Nevertheless, these pioneering psychophysical studies performed in very few volunteers provided the first insight into the topographical variation in thermal sensation and heated or cooled metallic rods may still be used for qualitative sensory testing in clinical settings and specific mapping purposes (53, 65). A useful variant of the metallic rods has

been developed for bedside assessment of thermal sensitivity in the neurological clinic (25). Four different materials – copper, stainless steel, glass and polyvinyl chloride – serve as differential heat sinks when applied to the skin at ambient temperature. These inexpensive thermal disks allow a rough assessment of thermal sensitivity on the skin including the facial skin. Based on similar principles, thermal rolls have also been used to qualitative assessment and mapping of altered thermal sensitivity. The rolls are heated or cooled in thermo-regulated water baths and are gradually moved from normal skin towards the affected area in a mapping procedure (Fig. 7). The patient notes when there is a change in the thermal sensation, i.e., hypoesthesia or hyperesthesia. This allows the mapping of areas with disturbances in the thermal sensation (Fig. 7).

In earlier days, individualized aluminum thermodes were also developed and fitted to the hard palate from the gum line to the soft palate. Thus, the stimulus area of such thermodes is approximately between 19 and 23 cm^2 (147). Two copper tubes can be incorporated into the thermode to provide inflow and outflow of circulating water from water baths of different temperatures. With the use of this set-up temperatures at the hard palate can be adequately controlled in the 44–50 ^oC range (147). This technique where the mechanical impact on the hard palate remained constant demonstrated that thermal stimulation always produced a warm or hot sensation below 43 ^oC and always heat pain above 49 ^oC. Thus, threshold for heat pain sensations on the hard palate was estimated to be on average 46.6 ^oC. For obvious reasons, this research device was never intended to become a tool for extensive QST, but the principle of circulating water of different temperatures is still employed in some older focal thermal stimulators (56).

After-sensations, which may serve as an indirect measure of central sensitization (148, 149), can also be reported by the subjects after application of an ice cube intraorally at the buccal surface of the first molar. As soon as pain is experienced due to coldness, the stimulation can be discontinued and the subjects report any occurrence of after-sensation intraorally (150).

A number of different thermal contact stimulators have subsequently been developed allowing more precise control of the thermal stimulus (151-155). At present, the most widely used and commercially available stimulators for thermal QST adopt contact thermodes that function according to the Peltier principle (Fig. 8). These thermodes are precise and control small or large pulses or ramps of cooling or heating at the thermode testing surface. The contact area of such thermodes is usually in the range of 0.25 to 9 cm^2. When performing thermal QST within the orofacial area, the size of thermode must be small enough (1-4 cm^2) in order to be able to investigate the trigeminal nerve distributions separately. For example, the mental nerve distribution is only ~ 2 cm in width, and the thermode surface should not cross its innervation borders when aiming to diagnose mental nerve or inferior alveolar nerve lesion (3, 4, 11). The smallest thermodes available are used for testing intraoral sites (Figure 8B).

In a contact thermode, the heating or cooling element is a thermoelectrical unit that is a series of thermocouples in parallel. When current is applied, the temperature at the ends of the thermocouples charges in opposite direction. This so-called Peltier effect is exploited to produce a set temperature, providing ramps of slowly increasing or decreasing temperatures, or pulses of cooling or heating (35). Thus, the stimulus configuration can be tailored for the exact purpose of the study and it is even possible to produce a tonic heat stimulus by manipulation of the number of thermodes, interstimulus intervals and stimulus intensity (156, 157). In the clinic, where thermal QST is most often performed with the quick method of limits technique, it is recommended to use a slow rate of temperature change (e.g. 1 ℃/s) and a device capable of linear change of temperature (29, 33).

There are several major advantages of conducted thermal stimulation. First, the temperature can be raised linearly and maintained at a constant level and the temperature changes can occur without a synchronized mechanical stimulus. In addition, some of the thermal QST devices

currently available allow strict control and continuous measurement of the skin and thermode temperatures for internal control and calibration. Moreover, the thermal stimulator can actively cool down or warm up the stimulus area and thereby faster return the skin temperature to the initial baseline temperature. Finally, the stimulus area is well defined (158). However, there are still some disadvantages like the possible confounding effect of a tonic activation of mechanosensitive afferent fibers. Commercial thermal contact stimulators are available today, which also contain thermodes designed for use in the orofacial region. When applying orofacial thermal QST to the clinical diagnostics or scientific research, it is important to obtain reference values from healthy subjects with exactly the same device and settings, thermodes of the same size, and standard locations that will also be used in the patients: thermal thresholds vary according to the anatomical site, thermode size, and the stimulator settings (11, 13, 25, 29, 33, 36, 159).

Radiant heat stimulators have also been extensively used for thermal stimulation. Hardy et al. (160) used focused light bulbs (100 watt) and blackened the skin with India ink to reduce the reflection and increase the absorption of the light. The light energy was absorbed at the tissue surface in the form of a transient temperature increase, which then was distributed in the skin or oral mucosa mainly by conduction to activate superficial thermoreceptors. Later, various types of laser stimulators were used for thermal stimulation of the skin (161, 162). The main advantage of radiant heat stimulation compared to contact heat stimulation is the definite lack of a concomitant activation of mechanosensitive afferent fibers. Furthermore, laser radiation in the visible range (λ = 400–700 nm) can easily be transmitted through flexible optical fibers, which allow stimulation of almost any intraoral regions. However, CO_2 laser radiation in the infrared wavelength (λ = 10600 nm) must be transmitted through articulated arms, which effectively limits the stimulation to the anterior parts of the oral mucosa. Other advantages with laser stimulators include the possibility to emit a very brief pulse in the range from just a few ms to 200 ms which allows the recording of

time-locked electrophysiological responses like laser-evoked reflexes and brain potentials (163-171). Argon laser stimuli (λ = 488–515 nm), CO_2, copper vapour (λ = 578 nm), Neodymium-yttrium-aluminum-garnet (Nd-YAG) (λ = 1064 nm), and thulium-YAG (1800 nm) laser stimuli have up to now been used in the orofacial region to test thermal sensations (171-176). Reflection of the laser light is dependent on the wavelength, which should be taken into consideration if the thermal sensitivity of different tissue surfaces is to be compared (174). The main disadvantage with lasers is that they are expensive, require technical maintenance, and may involve a risk of tissue damage (skin burn). In addition, the actual skin temperatures evoked are not controlled with laser stimulators as in QST devices based on contact thermodes. Furthermore, only warm and heat pain modalities can be investigated with laser techniques that do not give information about the function of cool and cold pain sensory channels. New generations of more stable, smaller and cheaper diode lasers (e.g. Gal-nAs/GalAlAs) are now being developed and hold promise to be useful tools in quantitative sensory testing (177), and have been successfully used to selectively stimulate A-delta and C-fiber heat-sensitive afferents innervating orofacial tissues (178).

In summary, thermal stimulators can be divided into simple metallic rods or thermal disks and rolls suitable for bed-side / chair-side qualitative analysis of thermal sensory function, high-tech Peltier devices with contact thermal stimulation for detailed quantitative analysis of all four thermal sensory modalities, and lasers or focused light for radiant heat stimulation. Each stimulus device has its unique characteristics in terms of controllability of the thermal stimulus and contribution from mechanosensitive afferent fibers. However, it is important to emphasize that technical differences not only have a bearing on methodological aspects but also on the possibilities to study the underlying mechanisms of thermal sensation, i.e. the effect of temporal (pulse duration) or spatial summation (stimulus area size).

Electrical stimuli

Strictly speaking, electrical stimuli can not be considered a pure sensory stimulus modality but a brief description is included here. Electrical stimulation is known to bypass the peripheral tactile and nociceptive receptors and can be used for direct activation of the large diameter A-beta primary afferent nerve fibers in addition to other small primary afferent nerve fibers, that in pain conditions may mediate tactile-evoked pain sensations (i.e. allodynia) (24, 63, 179). Electrical stimuli can easily be applied to the skin, muscle and joint as well as oral mucosa (e.g. 180). Sensory detection, pain detection and pain summation thresholds can be assessed using small steps like 0.05–0.1 mA delivered from a constant current device. The electrode configuration will have significant influence on thresholds. Recently a circular anode and cathode probe (diameters: 0.3/0.7 mm) with stimulus duration of 0.5 ms has been used (150) but pulse duration and repetition in trains can be tailored to the specific purpose of the study. It has been claimed that a concentric electrode arrangement may be able to predominately stimulate nociceptive afferent fibers (181) and commercial devices are available that can selectively, if not specifically, activate different nerve fiber populations.

Chemical stimuli

The identification and description of the molecular receptors associated with peripheral nerve transduction (182) provide the basis for use of chemical substances to activate specific classes of somatosensory afferents. For example, capsaicin binds to the TRPV-1 receptors on C-fiber afferent terminals and response-dependent methods can be used to quantify the psychophysical responses (e.g. 183). Sophisticated studies with different concentrations of capsaicin have been used to assess intraoral sensitivity to burning pain (184-186). Also, the menthol receptor TRPM-8 has received interest given its perceived cooling effect and has been tested in psychophysical studies (187).

Interestingly, the application of menthol on the skin overlying the TMJ evokes a paradoxical heat sensation (180).

Potential influences on somatosensory function

There are numerous factors that influence the assessment of somatosensory function, for example anatomical site, sex and age of the subject, psychological factors (attention, distraction, motivation, anxiety, alertness etc), methodological factors (instructions to test subjects, training, gender of investigator) and the specific features of the psychophysical method and its parameters (rate of intensity change, probe/thermode size, interstimulus interval, step size, etc). In the following paragraphs some of the pertinent factors are briefly reviewed and the reader is referred to more comprehensive reviews (e.g. 24, 29, 33).

Influence of age

A number of different studies have examined the effect of age on somatosensory function including thermal sensations in the orofacial region. One study found that thermal sensibility in the orofacial region did not seem to change significantly from 20 years to 80 years (188). Another study reported that thermal sensitivity in the extremities and in particular the feet decreases with age but that the sensitivity on the lips changes more slowly and inconsistently (189). Meh and Denislic (190) showed that the warm–cold difference limen in the face increased slightly with increasing age and in accordance, Heft et al. (191) reported a modest change in warming and cooling perception at the upper lip and chin with increased age. Dyck et al. (25) found no significant change in thermal sensitivity in the forehead or lip when 326 healthy subjects from 10 years to more than 80 years were tested. A recent extensive study nevertheless found subtle changes over the life time also in

orofacial somatosensory function (8). Younger children (6–8 years) are generally less sensitive to thermal and mechanical stimuli than older children (9–12 years) whereas the younger children are more sensitive to painful stimuli (8). Moreover, older subjects (> 40 years) are less sensitive than younger adults in terms of thermal and mechanical stimuli (6, 7). Although a recent study on orofacial somatosensory function (101) did not indicate significant age-dependent changes, age may still be important to control for and reference values (e.g. extra- and intraorally) for all orofacial regions will be needed for the assessment of orofacial somatosensory function with QST (13, 192).

Influence of gender and sex hormones

Dyck et al. (25) in their extensive data did not find significant differences between genders in thermal sensitivity on the forehead or lips. Neither Meh and Denislic (190) nor Essick et al. (36) found a gender effect in warm–cold difference limens or cold thresholds on the face. Feine et al. (193) observed higher pain ratings of thermal stimuli applied to the lip in women and better discrimination between heat stimuli than men. In general, it seems to be a controversial issue to what extent there are robust gender-differences in somatosensory sensitivity including the orofacial area (194), but overall there is a strong trend that women have lower pain thresholds and report more pain to most stimulus modalities (for a review see 195). Rolke et al. (7) also noted significantly lower pain thresholds in women than in men whereas sensory thresholds not were gender-dependent. Blankenburg et al. (8) observed that girls were more sensitive only to thermal detection/pain and pressure pain. Several factors are recommended to be considered in the discussion of sex-related differences in somatosensory sensitivity: influence of fluctuations in gonadal hormones, age, race, ethnicity, culture, physical variables (height, weight, blood pressure), psychological and cognitive factors (belief, coping, mood etc) (196, 197). Further research is needed to address the question of sex-related differences in specific somatosensory modalities but it

seems to be an important factor to control for and sex-specific effects should be tested when calculating reference values for the orofacial region (101, 192).

Influence of test site

Topographical differences in thermal sensitivity have been extensively documented in the orofacial region. The first evidence came from the determination of small warm and cold spots (110, 144-146, 198). In general these classical studies showed that cold spots were more abundant (> 8/cm2) than warm spots (~1–2/cm2) in the orofacial region. The functional significance of these findings has, however, been challenged since temperature sensitive spots are not uniquely associated with single thermal end organs, and because of the powerful spatial summation of warmth and cool stimuli (56, 199). Nevertheless, the threshold for detecting cooling (expressed as temperature change from baseline temperature) is less than the threshold for detection warmth at all facial sites (36). In another study, twelve different oral and facial regions were tested for responsiveness to three different warm temperatures (39–43–45 °C) and three cold temperatures (14–19–24 °C). This study demonstrated that the vermilion border of the lip and the tongue tip are the most sensitive to warm stimuli whereas other intraoral regions are less sensitive than the face regions (56). Cold sensation shows a more uniform pattern of sensitivity but again points to a high sensitivity of both the vermilion border of the lip and the tongue tip (56). A detailed analysis of the thermal responsiveness has revealed that the tongue tip is the most sensitive region to thermal stimuli and demonstrates the largest dynamic responsiveness both compared to the vermilion border of the lip and the fingertip (53, 159, 192). There is also some evidence that the upper vermilion lip is more sensitive than the lower and that the hairy part of the lip is more sensitive to warmth than the vermilion border and the mucosal part (56). The responsiveness to cooling is equally good on the tongue tip, vermilion lip, mucosal lip and hairy lip and seems stronger than on the fingertip and face.

Thus, the oral mucosa is considered to be equipped differentially for the assessment of increases versus decreases in temperature, with the sense of cold better developed than the sense of warmth when tested by punctate stimuli. Therefore, the thermal perception in the oral cavity is complicated, and biophysical properties of the oral mucosa and skin as well as the heat conductivity of different orofacial tissues may play a significant role in these differences in addition to variations in the innervation densities (53, 159, 200).

In line with the studies on contact heat stimulation, the use of thermal argon-laser stimulation has demonstrated that the tongue tip is the most sensitive orofacial region with the lowest sensory threshold. Warm sensation is easily evoked when a short 200-ms laser pulse is applied to the tongue tip, lip skin and hand but not to the hard palate and buccal mucosa (174). Intraregional differences in thresholds can not be explained solely by different reflection of the argon laser light, which points towards true differences related to innervation density (200). More recently, Agostino et al. (201) found that the warm detection thresholds to CO2 laser stimuli are unrelated to the distance from the brain in contrast to the painful pin-prick perception, except that the upper lip has significantly lower warmth thresholds than all other tested body sites. These authors suggested a diffuse low density of warmth receptors to explain their findings.

Also for mechanical stimuli, substantial site-to-site differences have been found in the orofacial region (81, 94, 101, 103, 105, 111, 192, 202, 203).

In conclusion, significant regional differences in somatosensory function exist in the orofacial region with the tongue tip being particularly sensitive to warm, cold, and mechanical stimuli (83, 84, 101, 159, 192, 204). The vermilion of the lips is also very sensitive. Somatosensory sensitivity in general decreases as one moves posterolaterally from the oral opening (205). This observation indicates a need to establish separate reference values for specific orofacial sites.

Variability and reliability

It should be noted that many of the various psychophysical techniques have not yet been critically assessed for diagnostic sensitivity, specificity, and predictive values. However, studies on somatosensory sensitivity in the trigeminal region have reported acceptable to good test-retest variability (coefficient of variation around 20%) whereas the inter-individual variability is larger (coefficient of variation up to 50%) (172). In general, reviews indicate that the results of QST are highly dependent on methodology, but they are also reasonably reproducible over days and weeks in normal and nerve-injured subjects (44, 91). In accordance Agostinho et al. (206) noted that thermal QST is a reliable diagnostic tool with small day-to-day variations. Juhl et al. (150) reported fair to good reproducibility between repeated sessions for intraoral somatosensory function; however, some measures were significantly increased pointing to habituation or adaptation. Pigg et al. (101) specifically tested the reliability of intraoral QST and found acceptable to excellent inter- and intraexaminer variability for most tests in the comprehensive battery with warmth detection thresholds being the least reproducible and pressure pain thresholds the most reproducible. Furthermore, it was found the intraoral thermal thresholds did not vary significantly over a 6 week period (159).

Nevertheless, these findings underscore the value and importance of a control group or control site to follow the natural fluctuations of somatosensory function in the orofacial region.

Influence of orofacial pain conditions

This paragraph is not intended to be an exhaustive or systematic review of QST findings in orofacial pain conditions but merely to illustrate that different orofacial pain conditions do in fact influence QST findings and, therefore, characterization and quantitative analysis of somatosensory

function contains relevant diagnostic information. For a more in-depth review and discussion of QST findings in orofacial pain conditions and the relative diagnostic value of QST compared to qualitative clinical sensory testing and neurophysiological measures the reader is referred to reference No. 11-14, 71, 72, and 123.

Acute tissue damage and its effect on thermal sensitivity have been studied in detail following lower third molar extractions. The post-injury period following uncomplicated surgery (i.e., in the absence of nerve injury) does not reveal any significant changes in either cool or warm detection thresholds confined to the extraction site (179). This finding supports a previous study where Hansson et al. (207) found no change in thermal sensitivity 5–18 hours following extraction of third molars, with the exception for an increased reaction time to warm stimuli on the operated side. It was speculated that differences in stimulus rise time and stimulus area could account for the different results between warm detection thresholds and reaction time and that the underlying mechanism of this thermal refractoriness could be related to diffuse noxious inhibitory controls or related endogenous inhibitory processes. Recently, Juhl et al. (150) described a lack of changes in somatosensory function except for a persistence of mechanical hyperalgesia in the surgical area up to one month after removal of a wisdom tooth.

Patients with trigeminal nerve injury secondary to mandibular or zygomatic fractures or orthognathic surgery have been followed 6-12 months after the injury or surgery and in general they have elevated warm and cool detection thresholds within the injured trigeminal nerve distribution (3, 4, 208). No changes have been reported for the pressure pain threshold (209). A nerve section lesion to the mental or inferior alveolar nerve has also been associated with abnormal temperature sensation more than 15 month after the surgery in some patients (2 out of 5), whereas patients with nerve compression demonstrate normal thermal sensations (210). Bilateral sagittal split osteotomies (BSSO) of the mandible have been shown to be associated with a decreased ability to detect

changes in thermal sensation on the lip which may last up to 12 months after the surgery (4, 211). This duration of thermal impairment is significantly longer than changes for other sensory modalities like touch, vibration, and two-point discrimination (68). It was earlier suggested that differences in recovery rates between the different sensory modalities were determined largely by their relative dependence on functional innervation density. This could be related to the strong dependency of warmth perception on spatial summation mechanisms, requiring more recovery time to accumulate sufficient numbers of afferent fibers for warmth detection (68). More recently, in a detailed follow-up study including intraoperative neurophysiological monitoring of the inferior alveolar nerve function during BSSO, and 12-month follow-up with QST and neurophysiological investigations, it could be shown that the rate of somatosensory recovery critically depends on the type of surgical nerve injury. Demyelinating injuries are caused by compression and mainly affect tactile afferent fibers (with thick myelin sheath). These recover quickly and completely by 4 months whereas more severe axonal injuries (e.g. after partial laceration) give rise to more persistent abnormal thermal QST findings up to on year (4, 211). After initial recovery from orthognathic surgery or trauma to the trigeminal nerve, positive signs (gain in somatosensory function) like hyperesthesia, hyperalgesia, and allodynia have also been reported (e.g. 108, 120). In some studies it has been found that somatosensory deficits as measured with QST do not correlate consistently with the patients´ subjective reports of somatosensory changes (108, 120, 212), although there are also contradictory reports (3, 4, 211).

In more chronic or recurrent pain conditions, such as cluster headache, patients appear to have significantly higher warm detection thresholds than control subjects for most test sites in the frontal and maxillary region (213). Cervicogenic headache patients have higher warm and cool detection thresholds than control subjects at several facial sites and hand. In contrast, migraine patients do not have significantly different thermal thresholds compared to control subjects (213). Langemark et al.

(214) did not find any significant differences in thermal discriminative ability between patients with chronic tension-type headache and control subjects, but later warm detection thresholds in the temporal regions have been described to be slightly higher on the group level in patients with tension-type headache compared to control subjects (215). Thus, these group level findings suggest a generalized thermal sensory impairment in some types of headache. At present the clinical significance and diagnostic applicability of this pathophysiological finding is not established.

In patients suffering from painful temporomandibular disorders (TMD), Maixner et al. (216) found no difference in thermal detection thresholds in the face when compared to control subjects. This was taken as evidence that there is no peripheral sensitization of the thermal pathways in TMD patients. Price and Harkins (57) showed no difference in the slopes of S-R curves ranging from non-painful warmth to painful heat sensations. Thus, in TMD patients there is little evidence for a change in thermal sensations in the non-painful range whereas temporal summation mechanisms seem to underlie an increased responsiveness to thermal stimuli in the painful range (216). Some more recent studies have consistently indicated generalized disturbances in somatosensory function in different subsets of TMD patients (e.g. 63, 125, 217-223).

Relatively few studies have examined the somatosensory sensitivity in patients with a chronic burning mouth syndrome (BMS). An early QST study in BMS patients could not demonstrate specific changes in thermal sensitivity as assessed by a large contact heat thermode at the midline on the tongue and lips (77). However, thermal laser stimuli applied specifically to the tongue tip, which is the main site of clinical pain, demonstrated significantly higher thresholds compared to those of matched control subjects (175). More recent studies utilizing small contact thermodes of appropriate size for the study of lingual nerve distribution have shown thermal hypoesthesia to cooling and warming in the tongue mucosa of BMS patients (224-226), sometimes in association with decreased heat pain tolerance. This thermal hypoesthesia finding may be related to a focal

small fiber neuropathy of the tongue mucosa (227, 228). Other conditions with chronic neuropathic pain in the facial region also seem to be associated with elevated warm and cool detection thresholds (thermal hypoesthesia) when compared to the non-painful contralateral side (229) or reference values gathered from a healthy population (230). Eide and Rabben (231) in their study on 23 patients with neuropathic pain in the orofacial region found increased temperature thresholds on the painful facial skin in the subgroup of patients with nerve injuries whereas no changes in temperature thresholds were found in the patients with spontaneous types of pain. Several other studies of neuropathic orofacial pain conditions have indeed documented disturbances in somatosensory function (e.g. 232-234).

Patients with both symptomatic and idiopathic trigeminal neuralgia have increased thresholds to warm and cold stimuli (thermal hypoesthesia) on the affected side of the face compared to the contralateral control side (9, 118, 235-237). After radiofrequency thermocoagulation of the proximal root and gasserian ganglion, a procedure that specifically injures the thin myelinated and unmyelinated sensory fibers and their cell bodies (i.e. thermal afferents), trigeminal neuralgia patients demonstrate elevated thresholds for warming and cooling, but not for tactile stimuli for an extended period after the surgery. Also patients with post-herpetic neuralgia involving the ophthalmic nerve in the face have been shown to have significant increases in warmth and cold threshold compared to the unaffected side (238). These studies therefore strongly suggest that somatosensory abnormalities in the thermal sensation are a frequent finding in trigeminal neuralgia patients but also that not all patients may suffer from this deficit (25).

Atypical facial pain is considered a possible type of neuropathic pain and is often described as accompanied by facial flushing and swelling which could be related to autonomic dysfunction (239). Thus, QST of thermal function in addition to imaging techniques like thermography could be of interest to use in patients with various types of facial neuropathic pain. Recent studies on atypical

odontalgia and atypical facial pain have indeed identified changes in somatosensory function similar to those in neuropathic facial pain (77, 230) although some studies have not demonstrated such differences (240).

In conclusion, despite the mechanistically-different and heterogeneous types of orofacial pain conditions, somatosensory abnormalities of one or more modalities are frequently observed. So far there is no clear pattern of the direction of the differences, i.e., both gain and loss in somatosensory function can be encountered with a trend that chronic pain per se (e.g. of musculoskeletal origin) is more often associated with gain in function (hyperesthesia, hyperalgesia), while chronic pain conditions associated with nerve damage is associated with various degrees of sensory loss (hypoesthesia) that may occur simultaneously with positive somatosensory phenomena (hyperalgesia, allodynia). The spectrum of somatosensory changes indicate that a multimodality approach is needed, i.e., it may not suffice to examine only one single stimulus modality but a battery of QST is required to further the understanding and diagnosis of somatosensory dysfunction in orofacial pain conditions (9, 78).

Batteries for comprehensive somatosensory testing

A QST battery needs to assess different afferent nerve fiber functions separately, detect both somatosensory loss and gain (negative and positive signs), apply to different test sites, be well-described with operationalized criteria, and be reproducible. It has been argued that qualitative or semi-quantiative measures of dynamic and static allodynia, wind-up (temporal summation) as well as deep pain sensitivity are important to include in the assessment (6, 7). Although a number of well-designed studies have used comprehensive sensory testing protocols in various orofacial pain conditions, the most advanced in terms of standardization, collection of reference data from different test sites, processing of data and application in various painful conditions is the German

Research Network on Neuropathic Pain (DFNS) protocol (6-9) (Table 4). The feasibility of adapting the protocol to the orofacial region has been demonstrated recently (101), supporting recommendation of its use in future studies also within the orofacial region. Specifically, it has been shown that all 13 somatosensory tests could be performed on the apex of the tongue and facial gingiva in the upper jaw with moderate to excellent reliability for most measures. The duration of the intraoral examination per test site is in the range of 35 min which is a bit slower than on extraoral sites. Thus, it is fair to conclude that the DFNS protocol can, indeed, be used for a comprehensive examination of orofacial somatosensory function. However, some limitations need to be taken into account. Validation studies of the proposed QST protocol within the orofacial region will be needed to establish the diagnostic value of the DFNS protocol before final guidelines for clinical diagnostics can be given. It should also be noted that the current DFNS protocol (6, 7) has used only one testing site at the face: the lateral cheek which differs in many aspect from other trigeminal nerve distributions (205) and, as regards thermal QST, the published reference values for the face have been gathered using a rather large thermode (6). Thus, in future research, the psychophysical DFNS protocol for the orofacial region has to be tested against objective data on peripheral or central nervous system function, e.g., neurophysiological recordings, neuropathological examination of nerve fiber density within skin and mucosal biopsies, and functional brain imaging, and validated in various clinical orofacial pain patient populations. So far, it can be considered the best available choice to be used when more objective quantitative diagnostic methods are not available.

Briefly summarized, the current DFNS protocol includes the following procedures, some of them quantitative (QST) and others “semi-quantitative”.

1. Thermal detection and pain thresholds (Fig. 9A).

Detection thresholds for cool (CDT) and warm (WDT) are measured, followed by thermal sensory limen (TSL, the difference threshold for alternating cool and warm stimuli). Threshold for cold pain (CPT) and heat pain (HPT) are subsequently measured. For each of the threshold differences, three determinations are made at each site.

Note that thermal probes that have been used in the extremities and face in the original DFNS report (6) are too large to apply in most trigeminal distributions or intraorally due to their size and shape, and specific probes have been developed and are commercially available (Fig. 8b). The intraoral probe size is small and this will influence the thermal thresholds significantly due to minimal spatial summation (159), causing the threshold to be higher and more variable. Furthermore, the thermal probes for intraoral use need to be covered by plastic due to hygiene. In addition, it should be noted that in the measurement of TSL, the reaction time error inherent in the method of limits is doubled.

2. Tactile detection threshold (Fig. 9B).

The mechanical detection threshold (MDT) is measured with von Frey hairs using a modified "method of limits". Five threshold determinations are made, each with a series of ascending and descending stimulus intensities. The final threshold is the geometric mean of these five series.

Note that mechanical stimulation with constant-force stimulators (e.g., von Frey nylon filaments or glass-fiber) require that they are applied perpendicular to the surface (79). This will make it difficult to stimulate posterior intraoral regions. Another concern is that the higher forces may cause damage to the oral mucosa and therefore the cut-off threshold may need to be lowered.

3. Mechanical pain threshold (Figure 9C).

Measurement of the mechanical pain threshold (MPT) is performed with custom-made weighted pinprick stimuli, again using a modified "method of limits". Five threshold determinations are made, each with a series of ascending and descending stimulus intensities. The final threshold is the geometric mean of these five series. These probes function properly only when applied parallel with gravity. This feature, along with the size of the devices, limits the orofacial regions that can be tested. Specific probes for intraoral use should be developed.

4. S-R-functions: Mechanical pain sensitivity and dynamic mechanical allodynia.

Mechanical pain sensitivity is performed using weighted pinprick stimuli of different stimulus intensities so that a stimulus-response function is obtained for pinprick-evoked pain. Seven stimuli are applied in a randomized order, five times each at each site, and the subject is asked to give a numerical pain rating for each stimulus. Dynamic mechanical allodynia is performed within the same test procedure, as moving innocuous stimuli (Q-tip, cotton wisp, and soft brush; Figure 9D-F) are inserted among the pinprick stimuli in the randomized protocol. A total of 50 stimuli, tactile and pinprick, are delivered at each site with the subject giving numerical pain ratings for each stimulus.

5. Temporal summation of pain.

In this test, 10 pinprick stimuli of the same intensity are repeated at the same interstimulus interval (1 Hz) and the subject is asked to give a pain rating on a numerical rating scale for each stimulus which is then compared to the pain rating for a single stimulus. Each series of 10 stimuli is repeated 5 times at the same site, but the location within the site is changed slightly between each set of stimuli in order to avoid stimulating exactly the same point twice.

6. Vibration detection threshold (Fig. 9G).

This "semi-quantitative" test is performed usually with vibrating tuning forks placed over a bony prominence in the control and test areas. Vibration threshold is determined with three series of descending stimulus intensities.

Note that vibratory stimuli are not easily applied on all locations of the face or within the oral cavity, however, it is possible to stimulate the most anterior parts e.g. apex of the tongue, facial gingiva. Another issue is related to vibration sensitive mechanoreceptors within the oral cavity. The base of the tongue has been shown to have Pacini-corpuscles but other areas inside the mouth and on the face have none (94, 241).

7. Pressure pain detection threshold (Fig. 9H).

The final test in the protocol is performed with either a pressure algometer or pressure gauge device with a probe area of 1 cm^2. The threshold is determined with 3 series of ascending stimulus intensities, each applied as a slowly (50 kPa / s) increasing ramp.

Proposals for assessment of somatosensory function in the orofacial region

Clinical chair-side examination

Currently, there are no validated guidelines for examinations of orofacial somatosensory sensitivity in the clinic (14). This is a proposal for screening procedures that can be done without the need for sophisticated stimulators (Table 5). First, patients can be asked to report their experience of spontaneous pain, dysesthesia, and paresthesia and of stimulus-dependent pain evoked by natural intraoral or extraoral stimuli. Outcome is dichotomous either as "absent" or "present". Alternatively, outcome can be assessed on categorical scales like 0 = never, 1 = hardly noticed, 2 = slightly, 3 = moderately, 4 = strongly and 5 = very strongly (242). Thereafter, a comparison of sensitivity

between the painful and the contralateral sides can be made by applying the following stimuli to the intraoral sites: Touch evoked by a cotton swab (area approximately 3 x 3 mm), a cold steel instrument (approximately 5 x 5 mm surface of a dental spatula kept cool in ice water or warm in hot water and dried off before application) and pain evoked by a sharp toothpick. The comparison outcome describes the painful side as either more (hypersensitive), less (hyposensitive), or equally sensitive (normosensitive) as the contralateral side to each of these stimuli. A recent pilot study has indicated that the test-retest and inter-examiner reliability is good for the suggested intraoral tests (243). Furthermore, it is possible to map the areas which respond differently to mechanical and thermal stimuli as compared with normal, non-painful areas, i.e., to construct somatosensory maps (Fig. 6).

Comprehensive technique

Based on the available information and published studies reviewed above, we propose to use the modified protocol (101) (Table 4) for a comprehensive analysis of orofacial somatosensory function. As for the RDC/TMD (244), other examination procedures and questionnaires can be added depending on the purpose of the study, but it is crucial that there is a core set of examination procedures that are adequately standardized and operationalized in order for the field to move forwards and to get comparable results from different centers. This does not mean that other protocols would be inferior but rather that the currently recommended one is considered by the authors the most pragmatic and clinically feasible QST protocol, based on extensive experience in somatosensory assessment (6, 7, 101, 221).

Future recommendations

The recommendations for screening (chair-side) and comprehensive (laboratory) testing of somatosensory function in the orofacial region are proposed to be used as the "gold standard" examination for the purpose of comparing data across different centers. In addition to comparisons between sides, center specific reference data bases will also be needed for clinical diagnostics on individual patient level. For specific research purposes there may be a need to include additional psychophysical testing, for example, electrical stimuli may be useful (72). Also, inclusion of chemical stimuli (menthol / capsaicin) can be used to describe other aspects of trigeminal somatosensory function (180, 183). Furthermore, validation of the recommended somatosensory testing protocol against data recorded with objective and quantitative "gold standard methods" for neuropathy and neuropathic pain, i.e. neurophysiological and neuropathological investigations, in different orofacial pain conditions is mandatory in future studies.

Future research will show if some of the 13 tests in the comprehensive examination can be omitted because they do not provide additional information or are strongly correlated with other measures. However, we recommend that the exclusion of any test be based on research data and therefore it is premature at this stage.

Conclusions

The first version of guidelines will allow standardized collection of data from the orofacial area. They will also provide guidelines for collection of data from the intraoral region. The clinical utility of this testing protocol is not currently known, but it generally holds promise in helping to differentiate neuropathic orofacial pain states from other chronic pain conditions. A coordinated effort at multiple clinical centers around the world can help accelerate this process and could potentially make substantial progress in the diagnosis, classification, pathophysiology, prognosis and ultimately management of complex orofacial pain disorders.

Table 1

Diagnostic criteria for neuropathic pain

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1. Pain with a distinct neuroanatomically plausible distribution

2. A history suggestive of a relevant lesion or disease affecting the peripheral or central somatosensory system

3. Demonstration of the distinct neuroanatomically plausible distribution by at least one confirmatory test*

4. Demonstration of the relevant lesion or disease by at least one confirmatory test

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Grading of certainty for the presence of neuropathic pain: Definite neuropathic pain: all criteria (1 to 4) fulfilled; Probable neuropathic pain: 1 and 2, plus either 3 or 4; Possible neuropathic pain: 1 and 2, without confirmatory evidence from 3 or 4.

*Clinical somatosensory examination may be supplemented by laboratory and objective tests to uncover subclinical abnormalities

Modified from (2, 5)

Table 2

Psychophysical approaches
Threshold
Sensory detection thresholds (the lowest stimulus intensity that the subject can detect)
Pain thresholds (the lowest stimulus intensity that the subject perceives as painful)
Tolerance thresholds (the highest stimulus intensity that the subject is able to endure)
Summation thresholds (the lowest stimulus intensity in a train of repeated stimuli, where the first stimuli are rated as non-painful, but the last stimuli are rated as painful)
Suprathreshold intensity ratings
Magnitude estimation
Stimulus-response curves
Mapping
Area
Grid
Center-of-gravity

*The exact definition of thresholds may vary depending on which specific psychophysical procedure has been used.

Table 3

Stimulus modalities		Peripheral sensory channel
Mechanical		
	Tactile	A-beta
	Two-point discrimination	A-beta
	Vibration	A-beta
	Pin-prick	A-delta, C
	Pinch	A-delta, C
	Deep pressure	A-delta, C
Thermal		
	Cold	A-delta
	Warm	C
	Heat pain	C, A-delta
	Cold pain	C, A-delta
Electrical		A-beta, A-delta, C
Chemical		
	Capsaicin	C
	Menthol	C

Table 4

Overview on proposed comprehensive test protocol (laboratory)

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1. Thermal detection and pain thresholds: cool, warm, warm–cool difference (thermal sensory limen), paradoxical heat sensations, cold pain, and heat pain (CDT, WDT, TSL, PHS, CPT, HPT).

2. Mechanical detection threshold (MDT).

3. Mechanical pain threshold (MPT).

4. S-R-functions: Mechanical pain sensitivity (MPS) and dynamic mechanical allodynia (DMA).

5. Temporal summation of pain as a wind-up ratio (WUR).

6. Vibration detection threshold (VDT).

7. Pressure pain detection threshold (PPT)

Based on the German Research Network on Neuropathic Pain (DFNS) (6, 7).

Table 5

Proposed screening examination of orofacial somatosensory function (chair-side)

Perceived changes evoked by natural stimuli (yes / no)

Extraoral

Touching the skin (yes / no)

Cold weather (yes / no)

Warm weather (yes / no)

Intraoral

Touch by food or tooth-pressure (yes / no)

Cold food / liquids (yes / no)

Hot food / liquids (yes / no)

Spicy food (yes / no)

Application of

Tactile stimuli (cotton swab)

Pin-prick (tooth-pick)

Cold (spatula kept in ice water)

As an alternative to the dichotomous outcome (yes / no), a categorical scale like 0 = never, 1 = hardly noticed, 2 = slightly, 3 = moderately, 4 = strongly and 5 = very strongly can be used.

Legends to figures.

Fig. 1.

Determination of a warmth threshold with the use of the method of constant stimuli. The psychometric function is constructed by plotting the percentage of "yes" responses to repeated stimuli at several different temperatures. The threshold is the temperature, which is perceived 50% of the times. This corresponds to 34.2 ^{o}C in this example.

Fig. 2.

The method of limits with discrete thermal pulses is illustrated in A. A series of ascending (A) stimuli is presented and the transition point is noted. This is repeated and the threshold is the average of the transition points (mean = 34.6 ^{o}C). The staircase method is shown in B. Initially, the step size is for example 4 ^{o}C and is increased as long as the response is no "n", the intensity is decreased upon the first yes "y" and the step size reduced to 2 ^{o}C. By reversing the stimulus intensity upon a change in response and by reducing the step size, the threshold can be defined as the average of the transition points. In this example the threshold corresponds to 34.4 ^{o}C.

Fig. 3.

Schematical presentation of the method of limits with a continuous thermal stimulus, which starts from the baseline at 30 ^{o}C and increases with a ramp of 1 ^{o}C/s. The subject pushes a stop bottom when warmth is perceived and the temperature ramps down to baseline. In this example the warmth threshold corresponds to 34.9 ^{o}C. This technique is sensitive to the reaction time of the test subject.

Fig. 4.

Principal organization of data in a 2 x 2 table according to the sensory decision theory. The numbers indicate the frequency of subject responses (”hot” or ”warm”) when a for example a 42 ^{o}C or 34 ^{o}C stimulus is applied in random order. The discriminability is related to the difference between hit and false affirmative rates and the response bias measure is related to the sum of the hit and false affirmative rates.

Fig. 5.

An example of a stimulus-response curve where the perceived warmth of the different thermal stimuli is rated on a 100-mm visual analogue scale (VAS) ranging from “not warm” to “extremely warm”. A power function can be fitted to the data set.

Fig .6.

Illustration of a mapping procedure with a brush and tactile stimulus.

Fig. 7.

Examples of simple thermal stimulators. The thermal roll is stored in a constant-temperature water bath. The test subject indicates whether the thermal sensation is changing when the roll is slowly moved.

Fig. 8.

Illustration of a commercial contact thermal system based on the Peltier principle. The thermode is available in different sizes (A and B). Different test algorithms for determination of warmth and cold thresholds are available with this set-up.

Fig. 9.

Comprehensive battery of QST applied to the oral mucosa. Cold detection threshold (CDT), Warmth detection threshold (WDT), warm-cool difference (thermal sensory limen, TSL), paradoxical heat sensation (PHS), Cold pain threshold (CPT), Heat pain threshold (HPT), Mechanical detection threshold (MDT), Mechanical pain threshold (MPT), Mechanical pain sensitivity (MPS), Wind-up ratio (WUR), Vibration detection threshold (VDT), Pressure pain threshold (PPT).

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Fig. 1.

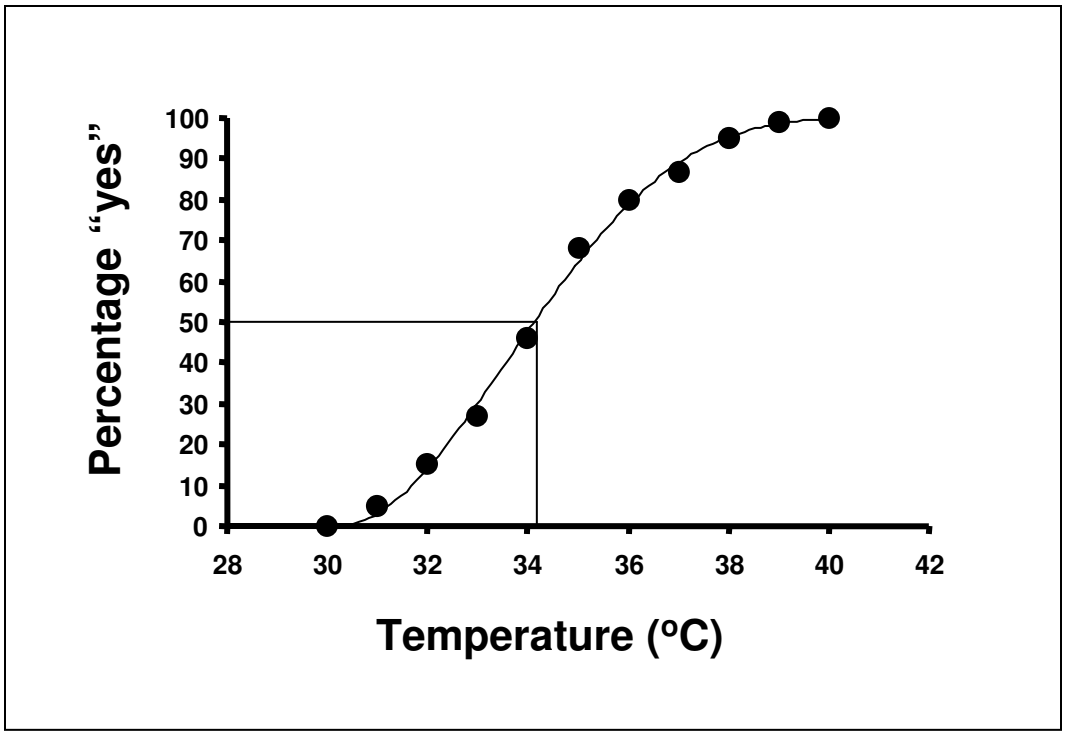
Percentage "yes"
100
90
80
70
60
50
40
30
20
10
0
28
30
32
34
36
38
40
42
Temperature (ºC)

Fig. 2.

A

	A	D	A	D	A	D	A	D	A	D
30.0	N									
30.5	N									
31.0	N									
31.5	N		N							
32.0	N		N		N					
32.5	N		N		N		N			
33.0	N		N		N		N		N	
33.5	N		N		N		N		N	
34.0	N	N	N		N		N	N	Y	N
34.5	N	Y	N	N	Y	N	Y	Y		Y
35.0	N	Y	N	Y		Y		Y		Y
35.5	N	Y	Y	Y		Y		Y		Y
36.0	Y	Y		Y		Y		Y		
36.5		Y		Y		Y				
37.0		Y		Y						
37.5		Y		Y						
38.0		Y								
38.5		Y								
39.0										
39.5										
40.0										
	35.75	34.25	35.25	34.75	34.25	34.75	34.25	34.25	33.75	34.25

B

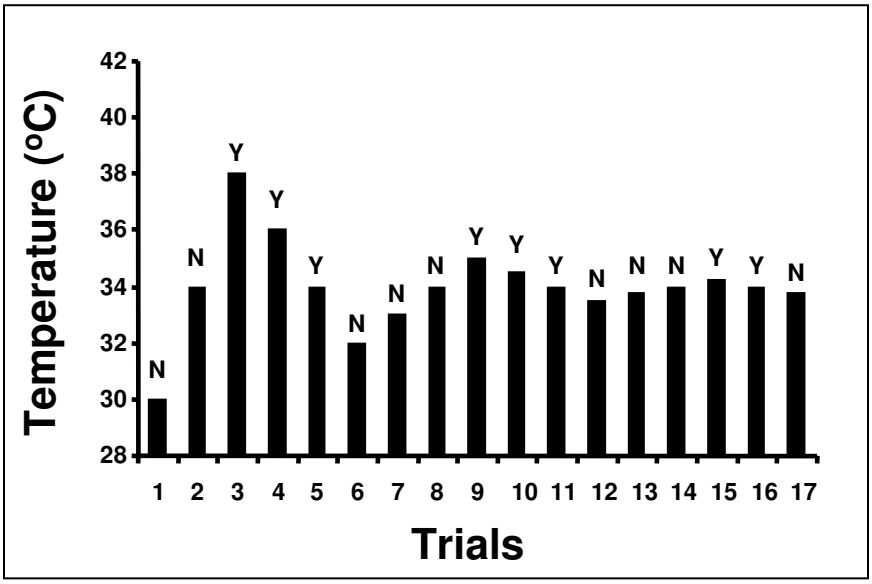

Fig. 3.

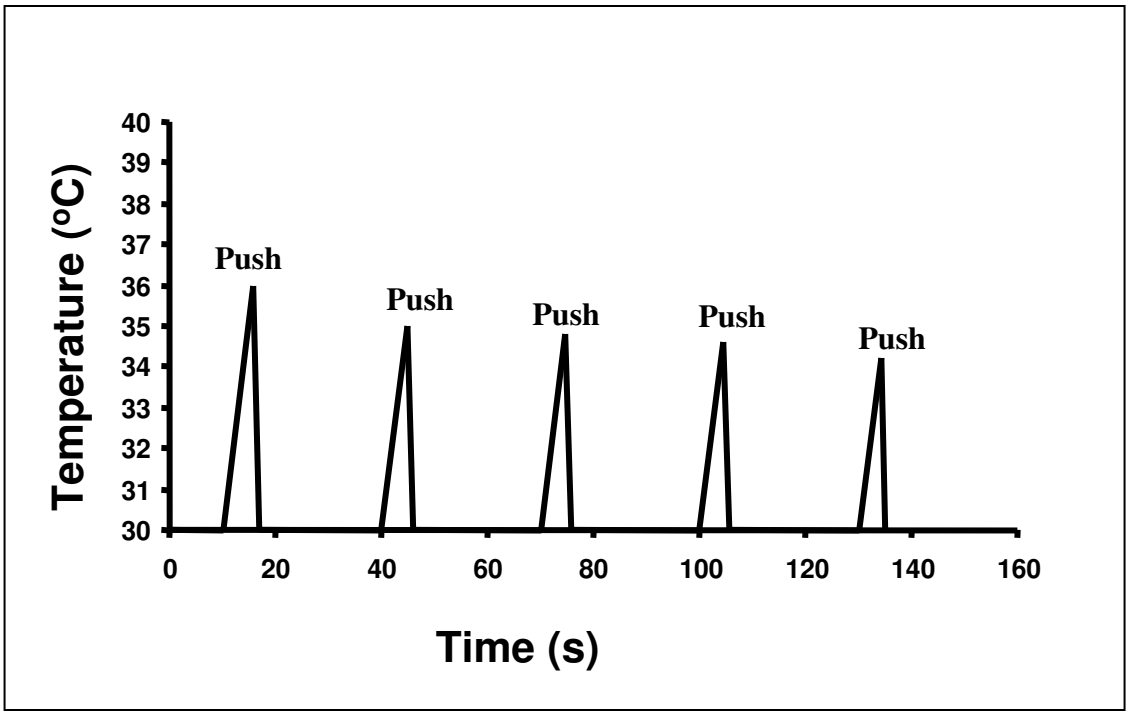
Temperature (°C)
40
39
38
37
36
35
34
33
32
31
30
Push
Push
Push
Push
Push
0
20
40
60
80
100
120
140
160
Time (s)

Fig. 4.

2 x 2 matrix	”Hot”	”Warm”
High stimulus 42 °C	Hit (sensitivity) 0.90	Miss 0.10
Low stimulus 34 °C	False affirmative 0.40	Correct rejection (specificity) 0.60

Fig. 5.

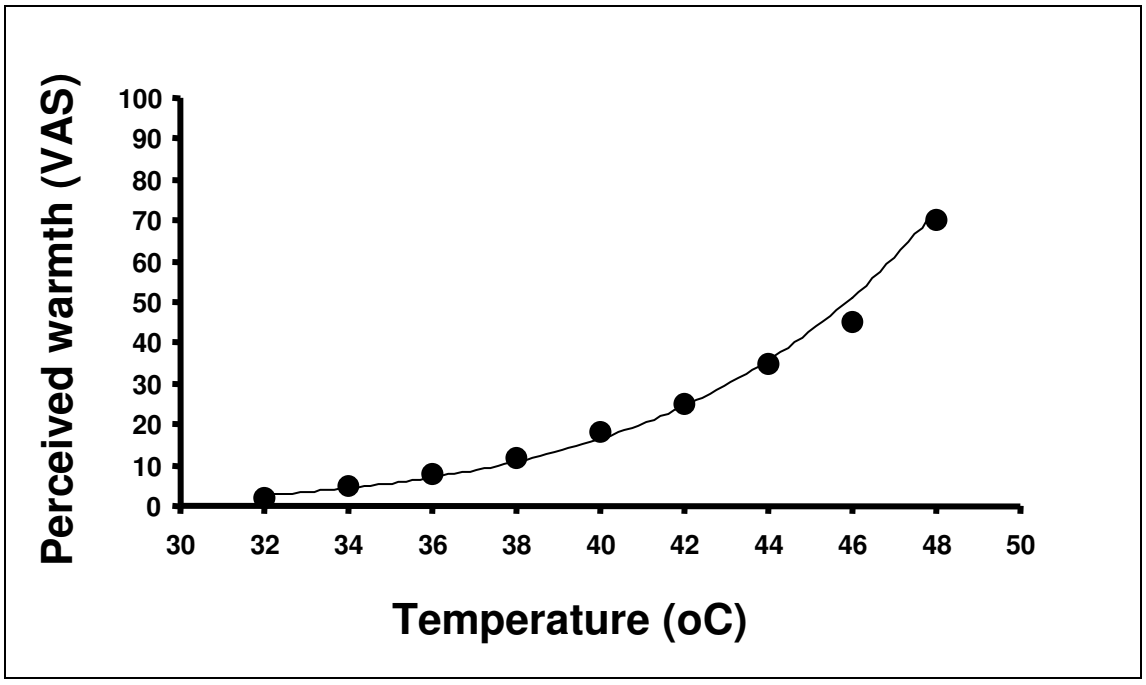
Perceived warmth (VAS)
100
90
80
70
60
50
40
30
20
10
0
30
32
34
36
38
40
42
44
46
48
50
Temperature (oC)

Fig. 6.

Fig. 7.

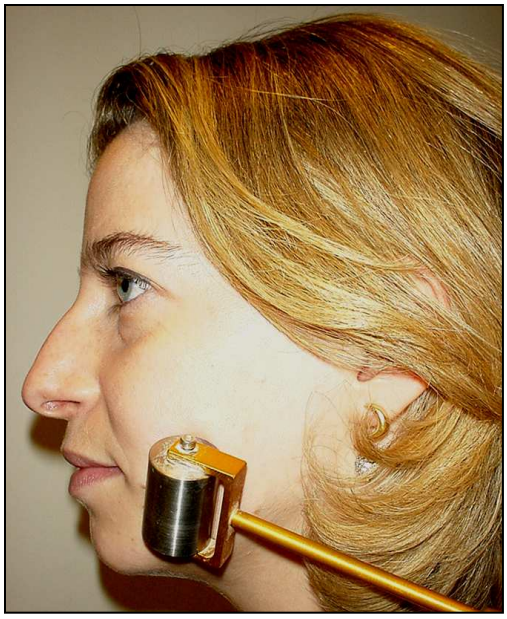

Fig. 8.

A

B

Fig. 9.


A
CDT, WDT, CPT, HPT, TSL, PHS
B
MDT
C
MPT, MPS, WUR
D
DMA
E
DMA
F
DMA
G
VDT
H
PPT